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RESEARCH

Real-world data of clazosentan in combination therapy for aneurysmal subarachnoid hemorrhage: a multicenter retrospective cohort study

Shinsuke Muraoka[1] · Takumi Asai[1] · Takahiko Fukui[1] · Shinji Ota[2] · Shinji Shimato[2] · Naoki Koketsu[3] · Toshihisa Nishizawa[1] · Yoshio Araki[4] · Ryuta Saito[5]

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Abstract

Aneurysmal subarachnoid hemorrhage (aSAH) may lead to cerebral vasospasm, significantly associated with morbidity and mortality. In double-blind, placebo-controlled phase 3 studies, clazosentan reduces cerebral vasospasm-related morbidity and all-cause mortality in patients with aSAH. There are no reports about the clinical efficacy of clazosentan combination therapy with some other drugs. Initially, we explored the efficacy of clazosentan combination therapy with cilostazol, statin, and antiepileptic drugs. Subsequently, we assessed the add-on effect of fasudil to clazosentan combination therapy for aSAH patients. This multicenter, retrospective, observational cohort study included Japanese patients with aSAH between June 2022 and March 2023. The primary outcome was the ordinal score on the modified Rankin Scale (mRS; range, 0–6, with elevated scores indicating greater disability) at discharge. Among the 47 cases (women 74.5%; age 64.4 ± 15.0 years) undergoing clazosentan combination therapy, 29 (61.7%) resulted in favorable outcomes. Overall, vasospasm occurred in 16 cases (34.0%), with four cases (8.5%) developing vasospasm-related delayed cerebral ischemia (DCI). Both hypotension and vasospasm-related DCI were related to unfavorable outcome at discharge. Fasudil were added in 18 (38.3%) cases. Despite adding fasudil to clazosentan combination therapy, the incidence of aSAH-related vasospasm did not decrease. Added-on fasudil to combination therapy related to pulmonary edema, vasospasm, and vasospasm-related DCI, and unfavorable outcomes. Clazosentan combination therapy could potentially result in favorable outcomes for aSAH patients to prevent post-aSAH vasospasm-related DCI. The add-on effect of fasudil to combination therapy did not demonstrate a significant impact in reducing aSAH-related vasospasm or improving outcomes at discharge.

Keywords Aneurysmal subarachnoid hemorrhage · Vasospasm · Clazosentan · Fasudil · Delayed cerebral ischemia · Prognosis

Introduction

Cerebral vasospasm is a significant cause of morbidity following aneurysmal subarachnoid hemorrhage (aSAH) [10, 17]. Angiographic vasospasm is observed in 70% of aSAH cases [6]. Approximately 40% of patients with cerebral vasospasm develop delayed ischemic neurological deficits, and 50% exhibit delayed cerebral ischemia (DCI) [8]. Cerebral vasospasm may be present as early as 24 h after onset but often begins 3–4 days after aneurysm rupture and peaks 7–10 days later before spontaneously resolving after 21 days.

The pathogenesis of cerebral vasospasm is not fully understood. Cerebral vasospasm may be caused by the degradation of blood products in the subarachnoid and perivascular spaces [49]. Current management strategies include the administration of nimodipine [9], ozagrel sodium

✉ Shinsuke Muraoka
neuro-smuraoka@umin.ac.jp

1 Department of Neurosurgery, Kariya Toyota General Hospital, Kariya, Aichi, Japan

2 Department of Neurosurgery, Handa City Hospital, Handa, Aichi, Japan

3 Department of Neurosurgery, Tosei General Hospital, Seto, Aichi, Japan

4 Department of Neurosurgery, Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Nagoya, Aichi, Japan

5 Department of Neurosurgery, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan

[29], fasudil hydrochloride hydrate ("fasudil") [33, 38], statins [32], and cilostazol [37]. However, their therapeutic efficacy is unsatisfactory [7].

Previous studies have suggested that endothelin-1, a potent and persistent endogenous vasoconstrictor, plays a role in the development of cerebral vasospasm [51]. After aSAH onset, the concentration of endothelin increases in the cerebral arteries, thereby increasing the sensitivity to endothelin-1 and intracellular calcium concentration [19].

Clazosentan, a selective endothelin receptor antagonist, inhibits endothelin-mediated cerebral vasospasm [2]. Several trials have been conducted to evaluate the efficacy and safety of clazosentan for preventing or modulating cerebral vasospasm in patients with aSAH [12, 23–25, 41]. Clazosentan was recently assessed in placebo-controlled, randomized, double-blind studies in adult Japanese patients with aSAH and showed a significant reduction in cerebral vasospasm-related morbidity and all-cause mortality within six weeks post-aSAH [11].

There are no reports about the clinical efficacy of clazosentan in combination therapy with some other drugs for the prevention of aSAH-related vasospasm. In this study, initially we investigate the efficacy of clazosentan combination therapy with cilostazol, statin, and antiepileptic drugs (AEDs). Subsequently we evaluate the add-on effect of fasudil to clazosentan combination therapy in aSAH patients.

Methods

This multicenter, retrospective, observational cohort study used data from patients with aSAH to investigate real-world data of clazosentan in combination therapy regimens.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Kariya Toyota General Hospital (approval number: 846). All experiments were performed following the STROBE guidelines. The requirement for informed consent was waived because the analysis used anonymous clinical data obtained after each patient had agreed to treatment by providing written consent. Furthermore, we applied the opt-out method to obtain approval for this study using a poster approved by the Institutional Review Board.

Study design and population

The study populations were enrolled at the Department of Neurosurgery of three hospitals, including Kariya Toyota General Hospital, Handa City Hospital, and Tosei General Hospital, from June 2022 to March 2023. According to American Heart Association/American Stroke Association guidelines, aSAH was diagnosed by head CT, CT angiography (CTA), or digital subtraction angiography [5].

The inclusion criteria were as follows: (1) spontaneous aneurysmal SAH; (2) surgical clipping or coil embolization performed within 24 h after onset; and (3) clazosentan was administered during the perioperative period. The exclusion criteria were: (1) non-aneurysmal or traumatic SAH; (2) non-surgical intervention; and (3) clazosentan was not administered.

Clinical data collection

We used a data registration sheet. This sheet included the following information: age, sex, body mass index (BMI), comorbidities (hypertension, diabetes mellitus, dyslipidemia), past medical history (any stroke, heart disease, renal disease), smoking history, modified Rankin Scale (mRS) score before onset, World Federation of Neurosurgical Societies (WFNS) grade, Fisher group, preoperative laboratory data, preoperative cardiac function (left ventricular ejection fraction), preoperative respiratory complications, aneurysm site, surgical procedure, cerebrospinal fluid drainage, intraoperative fluid balance, intraoperative urine output, postoperative management (medication, laboratory data, fluid balance per 24 h, and urine output per 24 h), angiographic cerebral vasospasm, vasospasm-related DCI, and mRS at discharge. The difference between the concentration of serum albumin (⊿Alb), sodium (⊿Na), hemoglobin (⊿Hb), and hematocrit (⊿Hct) at the onset and lowest value in the postoperative two weeks was calculated.

Therapeutic protocol

All patients underwent microsurgical clipping or coil embolization within 24 h of onset. Postoperative medical therapy was typically initiated on postoperative day (POD) 1, including cilostazol (200 mg/day), pitavastatin (2 mg/day), and antiepileptic drugs (levetiracetam 1000 mg/day or perampanel hydrate 2 mg/day). These drugs were used for two or three postoperative weeks. Intravenous clazosentan administration (10 mg/h) was continued from POD 1 to POD 14. Given that the choice to incorporate fasudil (30 mg*3/day) or ozagrel sodium (80 mg/day) was at the attending physician's discretion, these drugs were concurrently administered with the initiation of postoperative clazosentan.

Enteral feeding or oral intake was initiated on POD 1. Head computed tomography (CT) angiography was performed in patients who had undergone surgical clipping, and digital subtraction angiography (DSA) was performed in patients who underwent coil embolization. Brain magnetic resonance imaging (MRI) and MR angiography were performed on POD 5, 10, and 15. Chest radiography was performed daily in the first postoperative week. Fluid balance was measured every 24 h until POD 15. If the daily fluid balance was negative, 500 mL extracellular fluid

loading was delivered during this period. In the case of pulmonary edema, furosemide (20–40 mg/day) or tolvaptan (7.5 mg–15 mg/day) was occasionally administered. In the case of hypotension, if urine output was within normal limits, dobutamine (1–5mcg/kg/min) or norepinephrine (0.05–0.3mcg/kg/min) treatment was initiated. When pulmonary edema was sufficient to increase oxygen demand even with diuretic use, clazosentan was discontinued rather than non-invasive positive pressure ventilation or ventilator management. Clazosentan was also discontinued if hypotension did not improve with dobutamine or norepinephrine administration.

Image assessment

Independent neurosurgeons or radiologists blinded to the clinical information reviewed consecutive imaging studies. Based on the initial preoperative CT angiography, angiographic cerebral vasospasm was defined as inner artery reduction ≥ 50%.

Outcomes

The primary outcome was the ordinal score on the modified Rankin Scale (mRS; range, 0 [no symptoms] to 6 [death] with elevated scores indicating greater disability) at discharge. Outcomes on the mRS were defined as favorable (0–2) or unfavorable (5–6). The secondary outcome was vasospasm and vasospasm-related DCI. DCI was described as a new high-intensity region on MRI between 4 and 20 days after SAH. It was assumed to be a recent infarction if it was not visible on admission and the immediate postoperative CT scans. MRI and CT angiography/DSA confirmed the cause of DCI related to cerebral vasospasm according to the following criteria [46, 47]:

1. No other cause underlying permanent or temporary focal neurological impairment, such as hypoxia, electrolyte imbalance, infection, hydrocephalus, or seizure.
2. The Glasgow Coma Scale score decreased by at least two points.
3. No brain injury related to the treatment itself.

In previous studies, treatment-associated adversities like hypotension and pulmonary edema were documented [11, 12]. Such adverse events were also evaluated as safety outcomes in our current study.

Statistical analysis

We used SPSS for Windows version 20.0 (IBM, Chicago, IL, USA) for all statistical analyses. Continuous variables are presented as the mean ± standard deviation, and categorical variables are described as percentages. The risk factors for vasospasm, pulmonary edema, hypotension, vasospasm-related DCI, and unfavorable outcome (mRS 5–6) were evaluated using the chi-square test or Mann–Whitney U test. Binary logistic regression analysis was performed to calculate the odds ratio (OR) and corresponding confidence interval (CI). Receiver operating characteristic (ROC) curves were plotted to determine the threshold value of each parameter for predicting pulmonary edema, hypotension, vasospasm, and vasospasm-related DCI. The sensitivity and specificity of each parameter were calculated to identify the optimal threshold values.

Statistical significance was set at $p < 0.05$. A model with an area under the ROC curve (AUC) score of more than 0.7 was evaluated as adequate or better.

Results

Patient characteristics

We used clazosentan for 47 patients with aSAH (women: 35, men: 12; age 64.4 ± 15.0 years) from June 2022 to March 2023. Patient characteristics are presented in Table 1. The mean body mass index was 22.5 ± 3.8 kg/m^2. Hypertension was observed in 20 cases (42.6%), diabetes mellitus in 1 case (2.1%), and dyslipidemia in 6 cases (12.8%), and a positive smoking history was reported in 11 cases (23.4%). The median WFNS grade was 2 (IQR: 2–4), and that of the Fisher group was 3. Aneurysms were located in the anterior communicating artery (14 cases, 29.8%), internal carotid artery-posterior communicating artery (13 cases, 27.7%), middle cerebral artery (12 cases, 25.5%), and vertebral artery/basilar artery (4 cases, 8.5%). These aneurysms were treated surgically (32 cases, 68.1%) or endovascularly (15 cases, 31.9%). Cerebral fluid drainage was required in 26 cases (55.3%).

Primary and secondary outcomes

Postoperative management information and clinical outcomes are presented in Table 2. Among the 47 cases, 29 (61.7%) obtained favorable outcomes, and 9 (19.1%) had unfavorable outcomes at discharge. Vasospasms occurred in 16 cases (34.0%), but vasospasm-related DCI was only reported in 4 cases (8.5%).

Univariate risk factors for unfavorable outcomes, vasospasm, and vasospasm-related DCI were assessed, and multivariate analysis was performed (Table 3). Unfavorable outcomes were significantly related to hypotension (OR 16.111, 95% CI 1.659–156.501; $p = 0.017$), and associated to vasospasm-related DCI (OR 9.000, 95% CI 0.982–82.496; $p = 0.052$).

Table 1 Patients characteristics

Age, years, mean (SD)	64.4 ± 15.0
Female	35 (74.5)
BMI, mean (SD)	22.5 ± 3.8
Previous comorbidities	
Hypertension	20 (42.6)
Diabetes mellitus	1 (2.1)
Dyslipidemia	6 (12.8)
Smoking history	11 (23.4)
Pre-onset mRS, median	0 [0–2]
aSAH information	
WFNS grade	
I	11 (23.4)
II	14 (29.8)
III	9 (19.1)
IV	6 (12.8)
V	7 (14.9)
Fisher group	
1 (focal thin SAH)	2 (4.3)
2 (diffuse thin SAH)	8 (17.0)
3 (thick SAH)	28 (59.6)
4 (focal or diffuse thin SAH with significant ICH or IVH)	9 (19.1)
Aneurysm site	
Acom	14 (29.8)
IC-Pcom	13 (27.7)
MCA	12 (25.5)
VA-BA	4 (8.5)
Other	4 (8.5)
Pulmonary complication on admission	3 (6.4)
Laboratory data on admission	
Albumin (g/dL), mean (SD)	4.18 ± 0.35
Sodium (mEq/L), mean (SD)	139.4 ± 3.1
Hemoglobin (g/dL)	13.2 ± 1.7
Hematocrit (%)	39.5 ± 4.3
Operative information	
Microsurgical clipping	32 (68.1)
CSF drainage	26 (55.3)

Values are *n* (%) unless otherwise stated

aSAH, aneurysmal subarachnoid hemorrhage; *Acom*, anterior communicating artery; *BMI*, Body mass index; *CSF* cerebrospinal fluid; *IC*, internal carotid artery; *ICH*, intracerebral hemorrhage; *IVH*, intraventricular hemorrhage; *MCA*, middle cerebral artery; *mRS*, modified Rankin Scale; *Pcom*, posterior communicating artery; *SD*, standard deviation; *VA-BA*, vertebral artery-basilar artery; *WFNS*, World Federation of Neurosurgical Societies

Table 2 Postoperative management and outcomes

Fluid balance (mL)	
First postoperative week, mean (SD)	48.9 ± 533.2
Two weeks, mean (SD)	-6.1 ± 567.8
Urine output (mL)	
First postoperative week, mean (SD)	1620.3 ± 631.3
Two weeks, mean (SD)	1693.1 ± 652.0
Laboratory data within the postoperative 2 weeks	
Minimum serum albumin (g/dL), mean (SD)	2.61 ± 0.46
⊿Alb (g/dl), mean (SD)	1.58 ± 0.44
Maximum serum sodium (mEq/L), mean (SD)	144.6 ± 4.7
Minimum serum sodium (mEq/L), mean (SD)	135.1 ± 4.1
⊿Na (mEq/l), mean (SD)	4.4 ± 5.0
Minimum hemoglobin (g/dL), mean (SD)	9.4 ± 1.4
⊿Hb (g/dL), mean (SD)	3.8 ± 1.6
Minimum hematocrit (%), mean (SD)	28.2 ± 4.0
⊿Hct (%), mean (SD)	11.4 ± 4.1
Used drugs	
Fasudil	18 (38.3)
Ozagrel	15 (31.9)
Cilostazol	37 (78.7)
Stain	34 (72.3)
AED	35 (74.5)
Frosemide or Tolvaptan	20 (42.6)
Clazosentan Discontinued	8 (17.0)
Complications	
Vasospmasm	16 (34.0)
Pulmonary edema	19 (40.4)
Hypotension	16 (34.0)
Vasospasm-related DCI	4 (8.5)
mRS at discharge	
mRS 0-2	29 (61.7)
mRS 5-6	9 (19.1)

Values are *n* (%) unless otherwise stated

AED, antiepileptic drugs; *Alb*, albumin; *DCI*, delayed cerebral infarction; *Hb*, hemoglobin; *Hct*, hematocrit; *mRS*, modified Rankin Scale; *Na*, sodium; *SD*, standard deviation

The risk factors for vasospasm were higher BMI (OR 4.976, 95% CI 1.183–20.923; $p = 0.029$), positive fluid balance (OR 1.017, 95% CI 1.002–1.033; $p = 0.028$), lower urine output within the first postoperative week (OR 1.027, 95% CI 1.000–1.055; $p = 0.050$), and lower urine output within the first two postoperative weeks (OR 0.973, 95% CI 0.946–1.000; $p = 0.049$). The risk factors for vasospasm-related DCI were clazosentan discontinuation (OR 294.105, 95% CI 0.356–∞; $p = 0.029$), positive fluid balance within the first postoperative week (OR 0.977, 95% CI 0.950–1.006; $p = 0.038$), and positive fluid balance within the first two postoperative weeks (OR 1.025, 95% CI 0.996–1.055; $p = 0.027$).

ROC curves were plotted to determine the threshold value of each parameter for predicting vasospasm and vasospasm-related DCI. The sensitivity and specificity of each parameter were calculated to identify the optimal threshold values (Table 4).

To assess the vasospasm risk factors, the cut-off value for fluid balance within the first postoperative week was

Table 3 Risk factors of vasospasm, vasospasm-related DCI, unfavorable outcome, pulmonary edema, and hypotension

			OR	95% CI	*p*-value
Unfavorable outcome (mRS 5-6)	+ N=9	- N=38			
Hypotension	7 (77.8)	8 (21.1)	16.111	1.659-156.501	0.017
Vasospasm-related DCI	2 (22.2)	2 (5.3)	9.000	0.982-82.496	0.052
Vasospasm	+ N=16	- N=31			
BMI, SD	23.6 ± 4.6	22.0 ± 3.4	4.976	1.183-20.923	0.029
Fluid balance within the postoperative first week, mL, SD	229 ± 381	-90 ± 454	1.017	1.002-1.033	0.028
Urine output within the postoperative first week, mL, SD	1494 ± 483	1774 ± 740	1.027	1.000-1.055	0.050
Total urine output, mL, SD	1558 ± 501	1852 ± 745	0.973	0.946-1.000	0.049
Vasospasm-related DCI	+ N=4	- N=43			
Fluid balance within the postoperative first week, mL, SD	350 ± 330	32 ± 508	0.977	0.950−1.006	0.038
Total fluid balance, mL, SD	452 ± 449	-42 ± 533	1.025	0.996−1.055	0.027
Clazosentan discontinuation	2 (50.0)	6 (21.4)	294.105	0.356−∞	0.029
Pulmonary edema	+ N=19	- N=28			
Age, years, SD	73.8 ± 11.4	58.0 ± 13.9	1.105	1.019−1.199	0.016
Total fluid balance, mL, SD	293 ± 475	-200 ± 494	1.003	1.000−1.005	0.029
min Alb, g/dL, SD	2.25 ± 0.27	2.87 ± 0.41	0.001	0.000-0.164	0.010
Clazosentan discontinuation	7 (36.8)	1 (3.6)	29.255	1.321−647.981	0.033
Frosemide or tolvaptan use	14 (73.7)	6 (21.4)	14.125	1.254−159.120	0.032
Hypotension	+ N=16	- N=31			
BMI, SD	20.8 ± 2.7	23.4 ± 4.1	0.599	0.373−0.963	0.034
WFNS grade, median, IQR	3.5 [2−5]	2 [1-3]	6.274	1.687−23.329	0.006
Urine output within the postoperative first week, mL, SD	1256 ± 372	1864 ± 698	0.995	0.991−0.998	0.005
min Alb, g/dL, SD	2.31 ± 0.37	2.77 ± 0.44	0.014	0.000−0.818	0.014
min Na, mEq/L, SD	136.9 ± 3.1	134.1 ± 4.2	1.906	1.064−3.412	0.030
⊿Hct, %, SD	10.6 ± 4.8	11.7 ± 3.6	0.236	0.071−0.784	0.018

Values are *n* (%) unless otherwise stated

Alb, albumin; *BMI*, body mass index; *CI*, confidence interval; *DCI*, delayed cerebral ischemia; *Hct*, hematocrit; *IQR*, interquartile range; *mRS*, modified Rankin Scale; *Na*, sodium; *OR*, odds ratio; *SD*, standard deviation; *WFN*S, World Federation of Neurological Societies

–25 mL (AUC 0.706, 95% CI 0.544–0.867; $p = 0.027$, sensitivity 0.867, specificity 0.552). The AUCs for the BMI, urine output within the first postoperative week, total urine output, and minimum albumin level were 0.610 (95% CI 0.431–0.790; $p = 0.235$), 0.580 (95% CI 0.409–0.752; $p = 0.386$), 0.591 (95% CI 0.420–0.762; $p = 0.328$), and 0.699 (95% CI 0.526–0.871; $p = 0.032$), respectively. Therefore, these parameters were unsuitable for the prediction of vasospasm.

To ingestigate the vasospasm-related DCI, the cut-off value for total fluid balance was 130 ml (AUC 0.762, 95% CI 0.548–0.976; $p = 0.086$, sensitivity 0.750, specificity 0.738). The AUC for fluid balance within the first postoperative week was 0.696 (95% CI 0.478–0.914; $p = 0.198$), which was unsuitable for predicting vasospasm-related DCI.

Fluid balance during the first postoperative week and the first two weeks were 58.9 ± 500.1 mL and -0.3 ± 540.1 mL, respectively. Urine output in the first postoperative week and during the first two weeks were 1657.3 ± 669.3 mL and 1726.8 ± 680.2 mL, respectively. The lowest serum albumin, sodium, hemoglobin, and hematocrit levels in the first two postoperative weeks were 2.61 ± 0.46 g/dL, 135.1 ± 4.1 mEq/L, 9.4 ± 1.4 g/dL, and 28.2 ± 4.0%, respectively. The ⊿Alb was 1.58 ± 0.44 g/dL, ⊿Na was 4.4 ± 5.0 mEq/L, ⊿Hb was 3.8 ± 1.6 g/dL, and ⊿Hct was 11.4 ± 4.1%.

Safety outcomes

Pulmonary complications were observed in 19 cases (40.4%) and hypotension in 16 cases (34.0%). Clazosentan

Table 4 Cut-off value of each parameter

		AUC	95% CI	*p*-value	Sensitivity	Specificity
Vasospasm						
BMI	21.7	0.610	0.431–0.790	0.235	0.667	0.586
Fluid balance within the postoperative first week, mL	–25	0.706	0.544–0.867	0.027	0.867	0.552
Urine output within the postoperative first week, mL	1950	0.580	0.409–0.752	0.386	0.933	0.690
Total urine output, mL	2400	0.591	0.420–0.762	0.328	1.000	0.759
min Alb, g/dl	2.45	0.699	0.526–0.871	0.032	0.667	0.759
Vasospasm-related DCI						
Fluid balance within the postoperative first week, mL	120	0.696	0.478–0.914	0.198	0.750	0.667
Total fluid balance, mL	130	0.762	0.548–0.976	0.086	0.750	0.738
Pulmonary edema						
Age, years	67	0.791	0.644–0.937	0.001	0.889	0.821
Total fluid balance, mL	–50	0.804	0.678–0.929	0.001	0.889	0.607
min Alb, g/dL	2.65	0.915	0.828–1.000	<0.001	1.000	0.786
Hypotension						
BMI	21.1	0.706	0.551–0.862	0.022	0.687	0.767
Urine output within the postoperative first week, mL	1350	0.773	0.639–0.907	0.003	0.687	0.800
min Alb, g/dL	2.65	0.772	0.632–0.912	0.003	0.875	0.667
min Na, mEq/L	135	0.692	0.537–0.847	0.034	0.875	0.533
⊿ Hct, %	11	0.603	0.424–0.782	0.091	0.812	0.633

Alb, albumin; *AUC*, area under the curve; *BMI*, body mass index; *CI*, confidential interval; *DCI*, delayed cerebral ischemia; *Hct*, hematocrit; *Na*, sodium

was discontinued owing to pulmonary complications in 8 cases (17.0%). Smoking history was significantly related to clazosentan discontinuation ($p = 0.049$). The reasons for clazosentan discontinuation were respiratory complication (7 cases), hypotension (3 cases), and brain edema (1 case).

Univariate risk factors for pulmonary edema and hypotension were assessed, and multivariate analysis was performed (Table 3). ROC curves were plotted to determine the threshold value of each parameter for predicting pulmonary edema, hypotension, vasospasm, and vasospasm-related DCI. The sensitivity and specificity of each parameter were calculated to identify the optimal threshold values (Table 4).

Older age (OR 1.105, 95% CI 1.019–1.199; $p = 0.016$), clazosentan discontinuation (OR 29.255, 95% CI 1.321–647.981; $p = 0.033$), positive fluid balance (OR 1.003, 95% CI 1.000–1.006, $p = 0.029$), and lower serum albumin levels (OR 0.001, 95% CI 0–0.164; $p = 0.010$) were significant independent risk factors for pulmonary edema. ROC analysis showed that the AUC was 0.791 (95% CI 0.644–0.937; $p = 0.001$), and the optimal cut-off value with the maximum sensitivity and specificity for age at pulmonary edema occurrence was 67 years old (sensitivity 0.889, specificity 0.821).

The optimal cut-off value with the highest sensitivity and specificity in the ROC curve for total fluid balance was -50 mL (AUC 0.804, 95% CI 0.678–0.929; $p = 0.001$, sensitivity 0.889, specificity 0.607). The cut-off value of the minimum serum albumin level was 2.65 g/dL (AUC 0.915, 95% CI 0.828–1.000; $p < 0.001$, sensitivity 1.000, specificity 0.786).

Lower BMI (OR 0.599, 95% CI 0.373–0.963, $p = 0.034$), higher WFNS grade (OR 6.274, 95% CI 1.687–23.329; $p = 0.006$), lower urine output within the first postoperative week (OR 0.995, 95% CI 0.991–0.998; $p = 0.005$), lower serum albumin levels (OR 0.014, 95% CI 0–0.818; $p = 0.040$), higher serum sodium levels (OR 1.906, 95% CI 1.064–3.412; $p = 0.030$), and lower delta hematocrit levels (OR 0.236, 95% CI 0.071–0.784; $p = 0.018$) were significant independent risk factors for hypotension.

The cut-off value for BMI was 21.1 kg/m^2 (AUC 0.706, 95% CI 0.551–0.862; $p = 0.022$, sensitivity 0.687, specificity 0.767). The cut-off value for urine output within the first postoperative week was 1350 mL (AUC 0.773, 95% CI 0.639–0.907; $p = 0.003$, sensitivity 0.687, specificity 0.800). The cut-off value for the minimum serum albumin level was 2.65 g/dL (AUC 0.772, 95% CI 0.632–0.912; $p = 0.003$, sensitivity 0.875, specificity 0.667). The AUCs for the minimum serum sodium and delta hematocrit levels were 0.692 (95% CI 0.537–0.847; $p = 0.034$) and 0.603 (95% CI 0.424–0.782; $p = 0.091$), respectively. Hence, these parameters were not suitable for the prediction of hypotension.

Add-on effect of fasudil to clazosentan combination therapy

Fasudil was incorporated into clazosentan combination therapy, resulting in "multidrug therapy" in 18 cases (38.3%). As depicted in Table 5, when comparing clazosentan combination therapy with multidrug therapy, a discrepancy in the patients' baseline characteristics was observed. Multidrug therapy was more prevalent in patients with higher BMI ($p=0.021$). Microsurgical clipping was executed in patients utilizing clazosentan combination therapy ($p=0.024$). The postoperative fluid balance was significantly higher in the multidrug therapy group ($p=0.022$). Multidrug therapy was associated with a probable increase in unfavorable outcomes (13.8% vs. 27.8%, $p=0.274$), aSAH-related vasospasm (24.1% vs. 44.4%, $p=0.202$), vasospasm-related DCI (3.4% vs. 16.7%, $p=0.150$). In multidrug therapy, continuous administration of clazosentan proved challenging (6.9% vs. 33.3%, $p=0.053$) due to complications associated with pulmonary edema (31.0% vs. 55.6%, $p=0.130$).

Representative case

A 68-year-old man was brought to the hospital by ambulance with a disturbance of consciousness. Head CT showed a massive SAH due to a ruptured anterior communicating artery aneurysm (Fig. 1A, B). He was classified as WFNS grade 5 and Fisher group 3. Chest radiography revealed aspiration pneumonia (Fig. 1 C). Endovascular treatment was performed, and cilostazol and levetiracetam were administered from POD 1. Chest radiography revealed that aspiration pneumonia improved on POD 2 (Fig. 2A). On the same day, extubation was performed, and clazosentan, fasudil, statins, and cilostazol were administered. His respiratory condition gradually worsened from POD 5 (Fig. 2B) because of pulmonary edema; ozagurel was administered from POD 6, and clazosentan was discontinued on POD 7. The pulmonary disease improved from POD 8 (Fig. 2C), and the patient did not require oxygen. Cerebrospinal fluid drainage using an indwelling spinal catheter was continued from POD 1 to POD 14. During the first two postoperative weeks, head MRI/MRA did not detect vasospasm (Fig. 2D–F). The patient was transferred to a rehabilitation hospital with an mRS score of 2.

Discussion

To our knowledge, this is the first report to assess the real-world data of clazosentan use in combination with other therapeutic drugs, such as ozagrel sodium, fasudil, cilostazol, statins, and AEDs.

In our study, although vasospasm occurred in one-third of cases, the incidence rate of vasospasm-related DCI was less than 10%, and about two-thirds had favorable outcomes. Pulmonary edema and hypotension occurred in about one-third of cases. Hypotension and vasospasm-related DCI were poor prognostic factors unrelated to older age or disease severity at aSAH onset.

Although fasudil was added to clazosentan combination therapy, the incidence of aSAH-related vasospasm did not decrease. On the contrary, the addition of fasudil seemed to generate a positive in–out balance and could potentially contribute to the emergence of pulmonary edema complications. Further, the inclusion of fasudil was associated with an uptick in the incidence of cerebral vasospasm, vasospasm-related DCI, and unfavorable outcomes.

Vasospasm, DCI, and outcomes

In our study, vasospasm occurred when urine output was low despite a daily positive balance in slightly obese patients. On the other hand, vasospasm-associated DCI occurred when a positive balance continued daily, regardless of urine output. In one-third of cases, vasospasm was observed, but less than 10% developed DCI. Previous studies estimated the incidence of vasospasm-related DCI to be 30% [5, 13]. Previous placebo-controlled, randomized, and double-blind studies showed that 10.7%–18.6% of unfavorable outcomes occurred within six weeks [11]. In our study, the incidence rates of vasospasm-related DCI and unfavorable outcomes were lower than those in previous reports.

There was no significant add-on effect of fasudil to clazosentan combination therapy in preventing aSAH-related vasospasm. On the contrary, the addition of fasudil seemed to generate a positive in–out balance and could potentially contribute to the emergence of pulmonary edema complications. Further, the inclusion of fasudil was associated with an uptick in the incidence of cerebral vasospasm, vasospasm-related DCI, and unfavorable outcomes. In case of clazosentan administration in patients with aSAH, it may be advisable not to use it with fasudil. If there are cases of difficulty maintaining patients on clazosentan, using fasudil as a switch drug in such cases may be feasible.

The mechanism of DCI

Both DCI and vasospasm result from physiological changes such as early brain injury, microcirculation disturbances, microthrombosis, neuroinflammation, and cortical spreading depolarization (CSD) [13].

Recent research has recognized neuroelectrical disturbances, especially CSD and epileptiform activity, as critical contributors to the onset of DCI following aSAH. These disturbances can lead to detrimental effects, such

Table 5 The add-on effect of fasudil to clazosentan

	Cla alone *N*=29	Cla+Fas *N*=18	Univariate analysis *p*-value	Multivariate analysis *p*-value	OR	95%CI
Age, years, mean (SD)	65.7 ± 14.5	62.3 ± 16.1	0.549			
Female	23 (79.3)	12 (66.7)	0.493	0.078		
BMI, mean (SD)	21.7 ± 3.4	23.8 ± 4.3	0.047	0.021	1.542	1.066−2.229
Prior comorbidities						
Hypertension	13 (44.8)	7 (38.9)	0.767			
Diabetes mellitus	1 (3.4)	0 (0)	1.000			
Dyslipidemia	4 (13.8)	2 (11.1)	1.000			
Smoking history	5 (17.2)	6 (33.3)	0.291			
WFNS grade			0.576			
I	7 (24.1)	4 (22.2)				
II	9 (31.0)	5 (27.8)				
III	6 (20.7)	3 (16.7)				
IV	4 (13.8)	2 (11.1)				
V	3 (10.3)	4 (22.2)				
Fisher group			0.780			
1	1 (3.4)	1 (5.6)				
2	6 (20.7)	2 (11.1)				
3	15 (51.7)	13 (72.2)				
4	7 (24.1)	2 (11.1)				
Operative information						
Microsurgical clipping	24 (82.8)	8 (44.4)	0.010	0.024	0.073	0.007−0.709
CSF drainage	13 (44.8)	13 (72.2)	0.080			
Postoperative fluid balance (mL)						
First postoperative week, mean (SD)	–70 ± 457	266 ± 511	0.039			
Two weeks, mean (SD)	–137 ± 528	220 ± 498	0.051	0.022	1.003	1.000−1.006
Postoperative urine output (mL)						
First postoperative week, mean (SD)	1629 ± 551	1702 ± 842	0.984			
Two weeks, mean (SD)	1699 ± 565	1771 ± 850	0.944			
Used drugs						
Cilostazol	22 (75.9)	15 (83.3)	0.719			
Stain	18 (62.1)	16 (88.9)	0.091			
AED	20 (69.0)	15 (83.3)	0.324			
Ozegrel	9 (31.0)	6 (33.3)	1.000			
Frosemide or Tolvaptan	12 (41.4)	8 (44.4)	1.000			
Clazosentan Discontinued	2 (6.9)	6 (33.3)	0.041	0.053	14.244	0.967−209.854
Complications						
Vasospmasm	7 (24.1)	8 (44.4)	0.202			
Pulmonary edema	9 (31.0)	10 (55.6)	0.130			
Hypotension	10 (34.5)	6 (33.3)	1.000			
Vasospasm-related DCI	1 (3.4)	3 (16.7)	0.150			
mRS at discharge			0.795			
mRS 0-2	18 (62.1)	11 (61.1)	1.000			
mRS 5-6	4 (13.8)	5 (27.8)	0.274			

Values are *n* (%) unless otherwise stated

AED, antiepileptic drugs; *BMI*, Body mass index; *CI*, confidential interval; *Cla*, clazosentan; *CSF*, cerebrospinal fluid; *DCI*, delayed cerebral ischemia; *Fas*, fasudil; *mRS*, modified Rankin Scale; *OR*, odds ratio; *SD*, standard deviation; *WFNS*, World Federation of Neurosurgical Societies

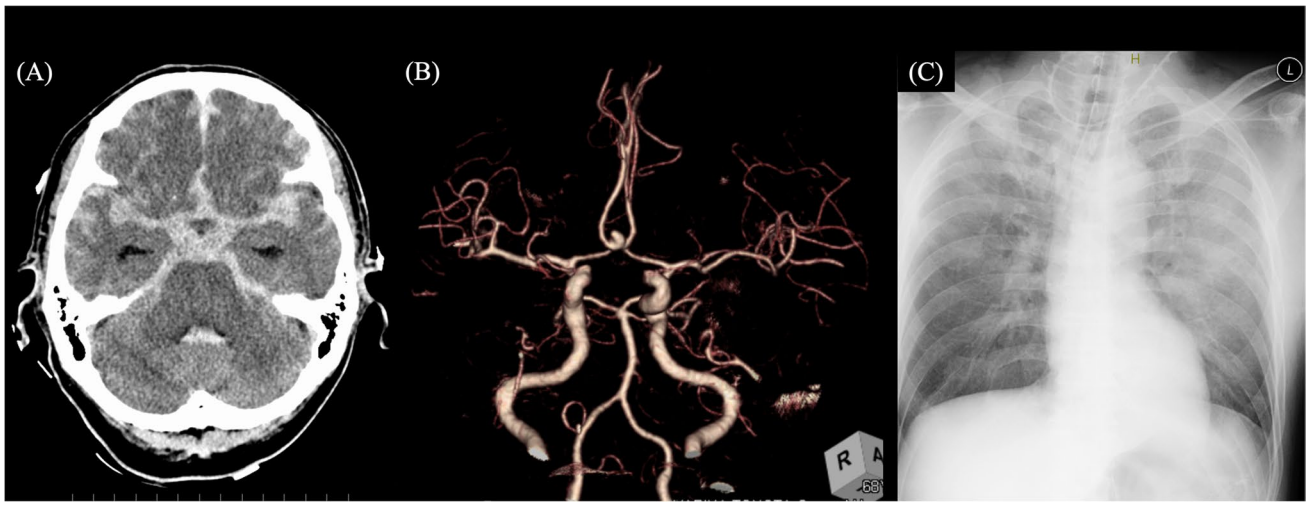

Fig. 1 Radiological findings on admission. (**A**) Head computed tomography (CT) showing massive subarachnoid hemorrhage in the basal cistern (Fisher group 3). (**B**) Head CT angiography showing a small aneurysm on the anterior communicating artery. (**C**) Chest X-ray showing aspiration pneumonia

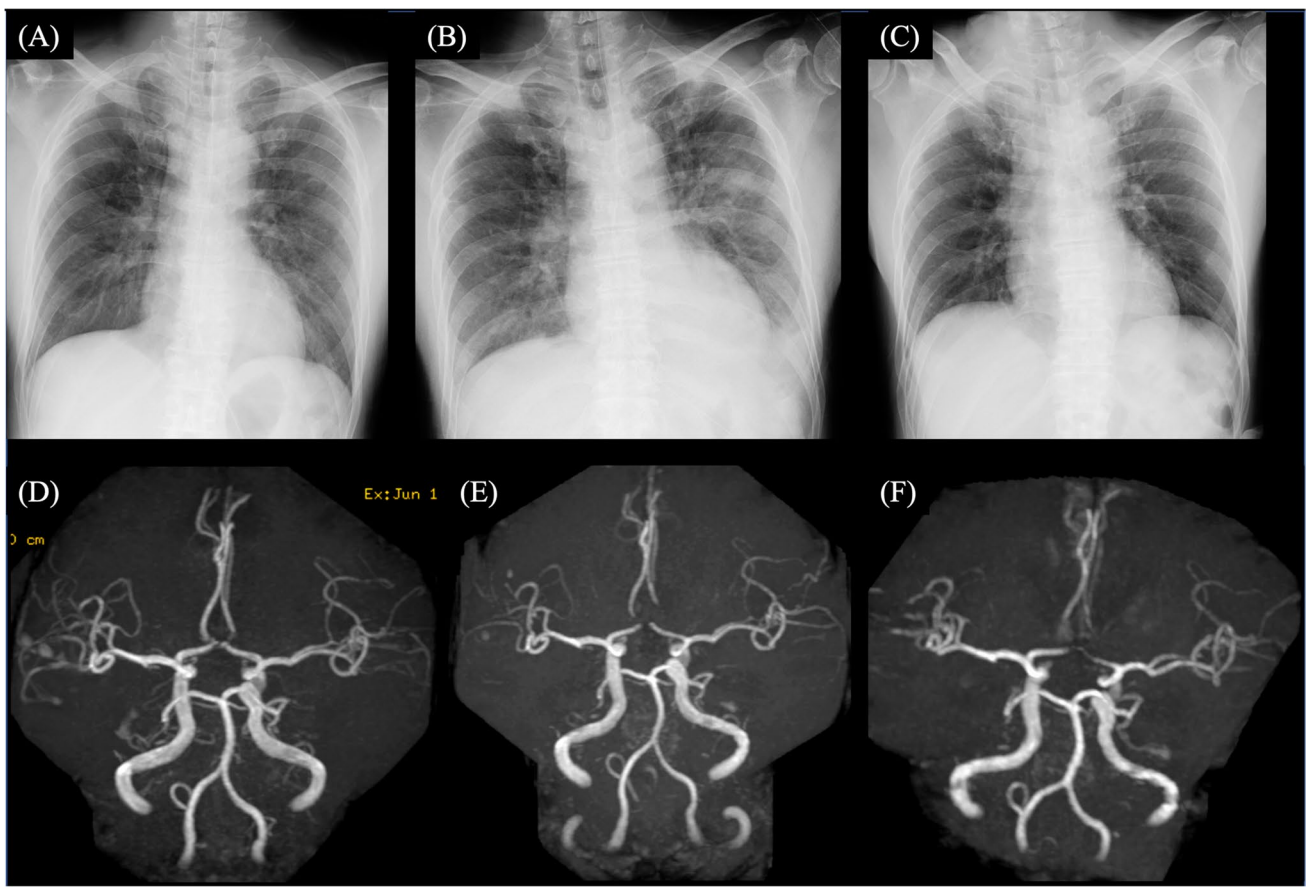

Fig. 2 Radiological clinical course. (**A**) Chest radiography showing improvement in aspiration pneumonia on postoperative day (POD) 2. (**B**) Pleural effusion and pulmonary edema were observed on POD 5. (**C**) After clazosentan discontinuation, the pulmonary condition improved smoothly on POD 8. (**D–F**) Head magnetic resonance angiography showing no vasospasm on POD 5, 10, and 15

as escalated metabolic demand, reversed neurovascular coupling inducing arteriolar vasoconstriction, microthrombus generation from platelet activation, and neuroinflammatory reactions, all potentially leading to DCI [35]. Some antiepileptic drugs have been reported to counteract both CSDs and epileptiform discharges, thus mitigating DCI [18]. Consequently, for this study, we opted to employ levetiracetam or perampanel—both reported as beneficial—as the foundational antiepileptic medications to enhance patient prognosis [36].

Accumulating evidence suggests that inflammation, particularly neuroinflammation, is associated with secondary outcomes following aSAH, including DCI and vasospasm [22, 26]. The multifaceted effects of statins, encompassing their anti-inflammatory properties, have been documented. Statins have demonstrated improvement in cerebral vasomotor reactivity, cerebral blood flow, and fibrinolytic activity [40]. The diminished endothelial nitric oxide synthase (eNOS) and endothelial function following SAH could be amplified by statin administration through activation of the phosphatidylinositol 3-kinase/Akt pathways, thereby mitigating vasospasm and enhancing cerebral vasomotor reactivity and patient outcomes [31, 34]. Given these considerations, statins were administered due to their projected beneficial effects, such as antioxidative, eNOS-inducing, endothelial cell-stabilizing, and anti-inflammatory properties in the treatment of cerebral vasospasm and DCI.

Cilostazol exhibited multifaceted effects on DCI reduction, encompassing the alleviation of angiographic vasospasm, enhancement of microcirculation [32], and attenuation of CSD through microcirculatory vasodilatation, which is mediated by both cyclic adenosine monophosphate and the upregulation of eNOS [16]. Moreover, cilostazol's mechanisms in inhibiting cerebral vasospasm pathogenesis predominantly involve several components: the suppression of lipid peroxidation [15], the decrease of reactive oxygen species [30], the induction of NO production [16], the prevention of endothelial damage [14, 50], and the hindrance of vascular smooth muscle proliferation [50]. Thus, in this study, we administered cilostazol to preempt microcirculation disturbances, microthrombosis, and CSD.

Hypotension

In healthy subjects, clazosentan has vasodilatory effects and slightly decreased systolic and diastolic blood pressure. However, this effect was not reported as clinically important [43, 44]. On the other hand, previous clinical studies of clazosentan reported that hypotension occurred in 10%–15% of patients [11, 12, 23–25]. In our study, 34% of cases showed hypotension. Therefore, perioperative combination therapy with clazosentan may lead to hypotension.

Cardiopulmonary dysfunction sometimes occurs after aSAH and is related to catecholamine release and sympathetic overstimulation [4, 42, 48]. Patients with a higher WFNS grade for aSAH are more likely to have complications of cardiopulmonary dysfunction. Echocardiography may show wall motion abnormality, and one of the most typical findings is apical ballooning and Takotsubo cardiomyopathy [20, 21, 27]. Treating stress cardiomyopathy with inotropes like milrinone or dobutamine could improve cardiac output and brain perfusion [4]. In our study, in slightly emaciated patients with a higher WFNS grade, if the serum albumin levels decrease despite a decrease in urine output during the perioperative period, these patients were likely to have hypotension. The clinical effects of dobutamine or norepinephrine to prevent hypotension while on perioperative clazosentan combination therapy must be evaluated.

Fluid retention

Fluid retention, mainly pulmonary edema, occurred in 40% of our cases (almost all had respiratory impairment requiring oxygen supplementation) and required diuretics. Previous clinical studies on clazosentan reported that respiratory complications occurred in 10–25% of patients [11, 12, 23–25]. In our study, respiratory failure did not improve despite diuretic use, leading to clazosentan discontinuation in approximately 15% of cases. Pulmonary edema occurred in cases with a positive fluid balance, with decreased serum albumin levels reflecting increased intravascular volume. It is essential to avoid managing older patients with a positive fluid balance day after day because of the possibility of respiratory compromise due to fluid retention. In this study, perioperative aSAH treatment management was primarily handled with euvolemia; however, if the fluid balance was positive on each postoperative day, pulmonary complications would likely occur with clazosentan. Intraoperative fluid balance has not been extensively discussed in managing patients with aSAH. Brandstrup et al. compared surgical patients who were given infusions to compensate for preoperative fluid deficits with those where surgeons focused solely on the intraoperative fluid balance. When patients undergoing surgery are given excessive infusions to compensate for fluid deficits, the fluid not excreted intraoperatively remains for at least six days after surgery, leading to complications such as heart failure and pulmonary edema [6].

Clazosentan is a peripheral vasodilator and may also increase capillary permeability. Excessive intraoperative and postoperative fluid infusions may result in pulmonary edema. Furthermore, some reports showed that positive fluid balance within the early postoperative phase was related to DCI and poor outcomes [1, 45]. For infusion management, it may be necessary to consider total fluid balance during surgery. However, the fluid balance may not precisely reflect blood or plasma volume. Some reports showed that measurement of the extravascular lung water

index, cardiac index, and pulmonary vascular permeability index using an invasive device was useful for identifying pulmonary edema in patients with aSAH [28, 29, 39]. Other less invasive monitoring parameters may be useful, such as body weight changes, cardiac output, and oxygen consumption. Further investigation will be needed on perioperative fluid management in patients with aSAH.

Limitations

This study has some limitations. First, numerous drugs were used to prevent vasospasm; therefore, these results cannot be attributed to clazosentan alone. However, in clazosentan combination therapy, it should be noted that vasospasm-related DCI occurred in only less than 10% of patients, regardless of aSAH severity or patient age. Second, this report is a small, retrospective study of patients with aSAH who underwent surgical treatment. A large, prospective cohort trial will be needed to evaluate the effectiveness of clazosentan in daily practice.

Conclusion

We first evaluated the efficacy of clazosentan in real clinical practice. Although vasospasm occurred in one-third of cases, the incidence rate of vasospasm-related DCI was less than 10%, and about two-thirds had favorable outcomes. Pulmonary edema and hypotension occurred in about one-third of cases. Hypotension and vasospasm-related DCI were poor prognostic factors unrelated to older age or disease severity at aSAH onset. Next, we investigated the add-on effect of fasudil on clazosentan. Adding fasudil to clazosentan combination therapy did not reduce the incidence rate of aSAH-related vasospasm. On the contrary, the addition of fasudil seemed to generate a positive in–out balance and could potentially contribute to the emergence of pulmonary edema complications. Further, the inclusion of fasudil was associated with an uptick in the incidence of cerebral vasospasm, vasospasm-related DCI, and unfavorable outcomes. Clazosentan may increase the risk of complications, such as hypotension and pulmonary edema. Perioperative fluid balance management may be critical for preventing unfavorable outcomes.

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Acquisition, analysis, and interpretation of data: S.M., T.F., S.O., S.S., N.K.

Drafting a significant portion of the manuscript or figures: S.M.

Supervision: R.S.

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Data availability The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study was approved by the Institutional Review Board of Kariya Toyota General Hospital (approval number: 846), and all procedures were conducted in accordance with the Declaration of Helsinki.

Consent to participate All experiments were performed according to the relevant guidelines and regulations. Patients were not required to provide informed consent for this study because the analysis used anonymous clinical data obtained after each patient had agreed to treatment by written consent. Furthermore, we used a poster to apply the opt-out method to obtain approval for this study. The Institutional Review Board of Kariya Toyota General Hospital approved the poster.

Competing interests The authors have no conflicts of interest to declare.

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